

Bulletin n:o 15 from the Department of Surgery

University of Lund, 221 85 Lund

1977

Portal hypertension

Studies on the problems of encephalopathy
and gastro-intestinal bleeding

GÖRAN SIMERT

From the Department of Surgery, University of Lund,
Lund, Sweden

PORTAL HYPERTENSION

Studies on the problems of encephalopathy and
gastro-intestinal bleeding

by

Göran Simert

Lund 1977



This thesis is based upon the following papers referred to in the text by their Roman numerals:

- I Simert, G., Lunderquist, A., Tylén, U., Vang, J.
Correlation between percutaneous transhepatic portography and clinical findings in 56 patients with portal hypertension.
Accepted for publication in Acta Chirurgica Scandinavica.
- II Rehnström, S., Simert, G., Hansson, J.A., Johnsson, G., Vang, J.
Chronic hepatic encephalopathy. A psychometrical study. Scand. J. Gastroent. 12, 305-311, 1977.
- III Simert, G., Nobin, A., Rosengren, E., Vang, J.
Neurotransmitter changes in the rat brain following portacaval anastomosis.
Accepted for publication in European Surgical Research.
- IV Simert, G., Persson, T., Vang, J.
Some factors predicting survival after portacaval shunt.
Accepted for publication in Annals of Surgery.
- V Vang, J., Simert, G., Hansson, J.A., Tylén, U., Bengmark, S.
Results of a modified distal spleno-renal shunt for portal hypertension.
Ann. Surg. 185, 224-228, 1977.

CONTENTS	Page No.
INTRODUCTION	7
Problems in portal hypertension	11
Purpose of the present investigation	11
MATERIAL	14
Clinical material	14
Experimental animals	15
METHODS	15
Examination methods	15
Statistical methods	20
RESULTS	23
Correlation between percutaneous trans- hepatic portography and clinical findings in 56 patients with portal hypertension.	23
Chronic hepatic encephalopathy. A psycho- metrical study.	25
Neurotransmitter changes in the rat brain following portacaval anastomosis.	25
Some factors predicting survival after portacaval shunt.	26
Results of a modified distal splenorenal shunt for portal hypertension.	27
DISCUSSION	29
CONCLUSIONS	41
ACKNOWLEDGEMENTS	42
REFERENCES	43

INTRODUCTION

Portal hypertension is a term used to designate an abnormally increased blood pressure in the portal venous system. The increase may be due to various factors, but the commonest cause is liver disease. Passive congestion of the portal system occurs. The congestion leads to the development of a collateral system conducting the blood round the liver to the systemic circulation. These changes result in the development of varices in the alimentary canal, and then mainly in the oesophagus and fundus ventriculi, ascites, hepatic encephalopathy, and sometimes in hypersplenism. Portal hypertension is also associated with a form of renal insufficiency, the hepatorenal syndrome. There might also be some connection between portal hypertension and chronic gastritis and chronic oesophagitis (Simert et al, 1976).

The term portal hypertension was introduced at the turn of the century by Gilbert et al (1899, 1906) and Pichancourt (1913). Heller (1904) was the first to detect the association between the formation of oesophageal varices and obstruction of the portal vein. Thompson et al (1937) found the pressure in the portal vein to be higher than in the systemic veins in patients with certain liver diseases.

The cause of portal hypertension is mainly obstruction to the escape of blood from the portal vein. The site of the portal block may be intra-hepatic or extra-hepatic.

The commonest cause of portal hypertension is liver cirrhosis of varying origin. The next in order of frequency is thrombosis of the portal vein, usually secondary to some infection (Shaldon et Sherlock 1962). Other, more uncommon causes are occlusion of the hepatic veins (Budd-Chiari syndrome) (Chiari 1899), schistosomiasis (Sherlock 1962) and compression of the portal vein by neoplasms or the like (Hurwitt et al 1954). A rare form of portal hypertension without gross obstruction to the portal flow has also been described (Mikkelsen et al 1965).

The collateral system in portal hypertension develops mainly from existing veins which are dilated to cope with the increased flow through them. Most of the collaterals normally exist also in the absence of portal hypertension (Thamm 1940). The most important pathways of the collaterals are: 1) the coronary vein - oesophageal veins - azygotic vein. 2) Haemorrhoidal veins. 3) Umbilical veins. 4) Retroperitoneal veins.

The collateral system is apt to give rise to mainly two complications, viz varices in the alimentary canal, chiefly in the oesophagus, with secondary haemorrhage and, second, together with the hepatic injury it may lead to a neuropsychiatric disorder generally known as hepatic encephalopathy. Attempts have been made to distinguish two forms of this encephalopathy, viz. "true" hepatic encephalopathy and porto-systemic encephalopathy (Kardel 1976). As is the case with most other manifestations of this syndrome, it is difficult to distinguish the effect of the liver disease from that of portal hypertension, and from now on the two terms for encephalopathy will be used synonymously in this book. The most widely known and also most advanced form of hepatic encephalopathy is hepatic coma. It may be combined with liver failure because of hepatocellular injury alone or in combination with overloading of the liver owing to dietary protein or gastrointestinal bleeding. Another, though less widely known, complication is that in the intervals between episodes of lowered level of wakefulness as well as in the absence of such episodes mental and neurologic disorders are common and more or less difficult to detect. In an investigation of 29 patients with liver cirrhosis and portal hypertension and about to be operated upon with portacaval shunt Kardel et al (1970) found the results of a psychometric test to be normal in only 6.

The etiology of encephalopathy in liver cirrhosis with portal hypertension has been the subject of much debate. The collaterals connecting the portal circulation with the systemic circulation imply that substances normally detoxicated in the liver may increase in concentration in the systemic circulation and thereby give rise to the cerebral phenomena observed. It was long thought that the precipitating factor was an increased amount of ammonia in the blood and the brain. The cerebral phenomena may be due to "power failure", i.e. disturbed production of energy in the brain, or a "transmission failure", i.e. disturbed transmission of impulses between the different cells. However, even considerable increases in the concentration of ammonia in animal experiments have failed to reveal any disturbance in the energy turnover of the brain. In recent years increasing attention has been directed to the possibility of "transmission failure", a theory assuming that ammonia does not play any decisive role, but rather that the changes in the neurotransmission may be due to alterations in the amino acid pattern in the blood in patients with liver disease (Fischer et al 1975).

Hitherto recognized important neurotransmitter substances in the CNS are dopamine, noradrenaline, serotonin and

acetylcholine. An important precursor of dopamine and nor-adrenaline is the amino acid tyrosine and precursor of serotonin the amino acid tryptophan. It may thus be possible that changes in blood and brain proteins and amino acids can induce changes in nerve transmitter concentrations in the CNS and also induce the syndrome hepatic encephalopathy. Such amino acid changes are regularly seen in patients with liver cirrhosis.

The most important clinical complication of portal hypertension is the increased risk of recurrent bleeding from the upper alimentary tract. But such bleeding is by no means a regular complication of portal hypertension. Of 115 patients with liver cirrhosis and oesophageal varices 28.6% later began to bleed (Baker et al 1959). Such bleeding worsens the prognosis, only 12 - 50% surviving for more than 1 year (Ratnoff and Patek 1942, Douglas and Snell et al 1950, Welch 1956, Ludington 1958). Efforts have therefore been made to prevent recurrent bleeding by surgery, mainly by portosystemic shunts. Of the other methods used and worth mentioning are ligation of the varices, transection of the stomach and oesophagus, oesophagogastrrectomy, ligation of the hepatic or splenic artery, and omentopexy. Transposition of the spleen to the thorax (Hästbacka 1971) or subcutis (Börjesson 1977) have been tried to a certain extent. In recent years interest has been increasing in sclerotherapy of the oesophageal varices, a method introduced by Crafoord and Frenckner in 1939. In 1973 Johnstone and Rodgers reported their 15 years experience with the method. Reports or large series with the use of this method have also been published by Denck and Sponer (1976) and Paquet et al (1977). But the value of the method for preventing further bleeding is still uncertain. A new method of sclerotherapy with the use of transhepatic catheterization of the coronary vein has been published by Lunderquist and Vang (1974) and the first report of the long-range effect of the method has just been published (Lunderquist et al 1977). The value of the method in the long term has not yet been established.

The hitherto commonest method for preventing recurrent bleeding from the alimentary tract in portal hypertension is surgical establishment of a portasystemic shunt. The portacaval shunt became clinically important after Whipple and Blakemore & Lord had published their results in 1945. For several decades this was the method most widely used. In large series the frequency of re-bleeding after the operation has ranged from 2 to 21% (Bengmark 1975). Despite its popularity, the method did not prolong survival of the patients with certainty. Three controlled randomised studies of therapeutic establishment of a portacaval shunt failed to show any prolongation of the survival of the patients

after the operation (Jackson et al 1973, Resnick et al 1974, Rueff et al 1976). This lack of any prolongation can probably be explained by overmortality from liver failure after the operation. In other words, the patients died from liver failure instead of from gastrointestinal bleeding. Such hepatic failure is probably due to a reduced flow of blood through the liver after establishment of a shunt. Various procedures have been tried to improve the effect of porto-systemic shunts. Earlier investigations, including the above mentioned controlled clinical trials, have shown that some patients with portal hypertension and bleeding from the upper alimentary tract never have a recurrence of haemorrhage; both Rueff et al and Resnick et al give a figure of about 30%. These patients can obviously not benefit from an operation directed against their portal hypertension. Therefore, if these low-risk patients could be identified and given medicinal treatment, it would probably substantially improve the results of treatment of patients with portal hypertension.

It might also be possible to improve the results of porta-caval shunt by acquirement of knowledge permitting better prediction of the duration of survival in a given case with and without surgical treatment. One might then, of course, avoid offering the patient operation unless there is reason to believe that it will prolong his survival. It is well known that the chance of survival depends to a large extent on liver function which can be measured with various liver function tests (Child and Turcotte 1964, Campbell et al 1973, Turcotte et al 1973, Malt et al 1976). Liver function has been assessed with Child's criteria (Child and Turcotte 1964). In this scale liver function is assessed according to the degree of muscular atrophy, the severity of encephalopathy, the serum bilirubin and albumin level, and the presence or absence of ascites. These variables are then combined to form a scale with three classes, where A denotes the best liver function and C the worst. This is, of course, only a crude method for predicting the chances of survival and, moreover, some of the variables overlap since there is a close co-variation between the factors measured.

One of the most effective ways of improving the prognosis of portal hypertension with recurrent bleeding from the upper alimentary tract would be to devise better operative procedures. Efforts have been made by many to improve porta-systemic shunts. Modifications of the original end-to-side portacaval shunt were the first to be made. Longmire (1950) suggested a side-to-side shunt. Several other types of shunt which, as far as flow is concerned, resemble a limited side-to-side shunt, such as a proximal

splenorenal shunt (Linton et al 1961) and the so-called H-graft shunt between the superior mesenteric artery and the vena cava (Drapanas 1972) have been tried. Some authors believe the proximal splenorenal shunt to offer no advantages over the original end-to-side shunt (Voorhees et al 1970, Bismuth et al 1974, Malt et al 1976), although some believe it to cause less encephalopathy than a portacaval shunt (Linton et al 1961, Hallenbeck et al 1963, Gill et al 1975, Pliam et al 1975). However, no controlled randomized studies of the problem is available. It is still too early to say anything definite about the relative value of the H-graft, but from a haemodynamically point of view, it resembles a proximal splenorenal shunt.

The idea of selective decompression of the oesophageal varices with preservation of the high pressure in the portal vein and the remaining portal flow to the liver led to the development of the distal splenorenal shunt. It was first described independently by Warren et al and by Texeira et al in 1967. If the use of this method could prevent recurrences of bleeding from the alimentary tract and at the same time preserve the portal flow through the liver, it may theoretically lower the number of deaths from hepatic failure after establishment of conventional portosystemic shunts.

Problems in portal hypertension

Problems connected with portal hypertension are many. Some of the most important are given below.

1. Prevention and reversal of liver cirrhosis.
2. Treatment of ascites.
3. Prevention and treatment of hepatorenal insufficiency.
4. Identification of patients with hepatic encephalopathy, prevention and treatment of this syndrome.
5. Treatment of bleeding from oesophagus and stomach.
 - a. How should we evaluate and identify patients with a great risk of recurrent bleeding?
 - b. How should the acute bleeding best be controlled?
 - c. What is the best available prophylaxis against recurrent bleeding and should it be individualized?
 - d. What criteria should be used in the selection of patients receiving prophylaxis against recurrent bleeding?

Purpose of the present investigation

In the present study interest was focused on some aspects of the most important problems in portal hypertension viz. encephalopathy and bleeding from the upper alimentary tract. In Part I an attempt is made to describe the spontaneous portosystemic shunts with the aid of percutaneous trans-hepatic portography and evaluate the frequency of the different locations and to study if there is any correlation

between gastrointestinal bleeding and liver function viz-a-viz degree of collateralization, localisation of collaterals and portal pressure. Since spontaneous extensive collateralization may theoretically reduce the risk of gastrointestinal bleeding but also include risks of reduced portal perfusion of the liver, spontaneous collaterals may be assumed to be of preventive value regarding bleeding but of negative value regarding liver function. The development of such spontaneous collaterals could thus some way or another have a prognostic significance.

Part II of the present series discusses the possibility of recognising mild hepatic encephalopathy with the aid of psychometric tests and compares the results of such tests with the clinical findings and routine electro-encephalographic recordings. Attention was also given to the question whether the results of the tests vary with the cause of the cirrhosis and whether alcoholism and liver damage differ in their direct effect on the brain. Interest was also focused on the possible significance of establishment of a porto-systemic shunt in the development of hepatic encephalopathy.

As better understanding of the pathophysiology of hepatic encephalopathy is necessary to improve the treatment of this complication and since the behaviour of neurotransmitter substances may play a role for the development of hepatic encephalopathy Part III of the present series is a study of the changes in the concentrations of the three important transmitter substances, serotonin, noradrenalin and dopamine, after establishment of a portacaval shunt in the rat, and, second, whether the regional distribution of such changes in the brain varies.

We also studied the effect of L-dopa on the neurotransmitter substances in animals with a portacaval shunt. L-dopa can probably reverse hepatic coma (Abramsky and Goldschmidt 1972, Fischer et al 1976). The effect of protein loading on the transmitter substances also received attention. The effect of a portacaval shunt on the rate of synthesis and accumulation of serotonin and its chief degradation product 5-HIAA (5-hydroxyindole acetic acid) was also examined. The purpose of these animal experiments was to test the theory that hepatic encephalopathy is due to a "transmission failure" in the CNS.

To make a better selection of patients to portosystemic shunt possible the problem of the Child classification and various factors that may predict survival was investigated in Part IV.

We also tried to improve portosystemic shunts and our experience with a modification of Warren's distal spleno-renal shunt and of the findings made at follow-up are discussed in Part V.

MATERIAL AND METHODS

Clinical material

Correlation between percutaneous transhepatic portography and clinical findings in 56 patients with portal hypertension (I): The material consisted of all the first 56 patients with portal hypertension examined with percutaneous transhepatic portography. The patients were thus in no way selected. In most of them portal hypertension had already been confirmed or suspected by other methods (e.g. endoscopically demonstrable oesophageal varices). In some of the 56 patients the indication for examination had been suspect intrahepatic tumour. In 55 of the patients the diagnosis of liver cirrhosis had been confirmed by biopsy. The remaining patient had so-called primary portal hypertension.

Chronic hepatic encephalopathy. A psychometrical study (II): The material consisted of 41 patients who had pathologically confirmed liver cirrhosis and who were attending the regular follow-up program for patients operated upon for portal hypertension or who had been referred to the department for further investigation of newly discovered portal hypertension. The cirrhosis was regarded as alcoholic in 18 of the patients, as definitely not alcoholic in 19, and of uncertain origin in four. Thirteen patients had a portacaval shunt; 11, a distal splenorenal shunt; and 5 had undergone subcutaneous transposition of the spleen. Twelve of the patients had portal hypertension, but had not been treated with the establishment of a shunt. In one of the studies the controls consisted of 15 patients defined as alcoholics and treated at the department of psychiatry in Lund in 1968 - 1972. No patients with suspect or verified liver damage were accepted as controls in that study.

Some factors predicting survival after portacaval shunt (IV): The hospital records of 315 patients operated upon with end-to-side portacaval shunt in Lund between 1951 and 1973 were studied. Only cases in which the patients had been operated upon electively i.e. patients who had not bled within the last 14 days before the operation, and in whom all the relevant variables had been measured, were accepted. 181 failed to meet these requirements. This left 134 for the present investigation.

Results of a modified distal splenorenal shunt for portal hypertension (V): The material consisted of 25 cases of histologically confirmed cirrhosis, bleeding from the upper alimentary tract and with verified oesophageal varices

and operated upon with establishment of a distal spleno-renal shunt between February 1970 and February 1973. The cases were consecutive and unselected in so far as all patients with upper gastrointestinal bleeding with portal hypertension that were operated upon within the period in question were included. Neither haemodynamic nor other factors were considered in the selection of the patients.

Experimental animals

Neurotransmitter changes in the rat brain following porta-caval anastomosis (III): Full-grown (270-400 g) male rats of the Wistar strain were used. They were kept in cages, 4 in each, and fed standard pellets and allowed water ad lib.

Examination methods

Correlation between percutaneous transhepatic portography and clinical findings in 56 patients with portal hypertension (I): Our method of percutaneous transhepatic portography is performed essentially according to the principles recommended by Wiechel (1971) and recently described in detail by Hoevels (1977). The method is briefly outlined below. See also Fig. I!

After local anaesthesia of a suitable intercostal space the liver is punctured by a needle inserted in the mid-axillary line and advanced towards the hepatic portal. The needle is withdrawn and the catheter is drawn back until its tip is situated in the right portal branch or one of its smaller branches.

With the aid of a guide wire the catheter is then advanced to the part of the splenic vein close to the hilus, and the first injection of 40 ml contrast medium is injected at a rate of 8 ml per second. The tip of the catheter may then be placed selectively in different branches of the portal tree according to the information desired.

From the roentgen examination the following variables were estimated: the flow through the oesophageal varices; visibility and size of coronary vein; filling of oesophageal varices from the coronary vein alone, and from the *venae gastricae breves* alone or from both the coronary vein and the *venae gastricae breves*; portal pressure; direction of flow through the portal vein; diameter of portal vein and of splenic vein; retrograde flow, if any, and largest diameter of the inferior mesenteric vein and the umbilical

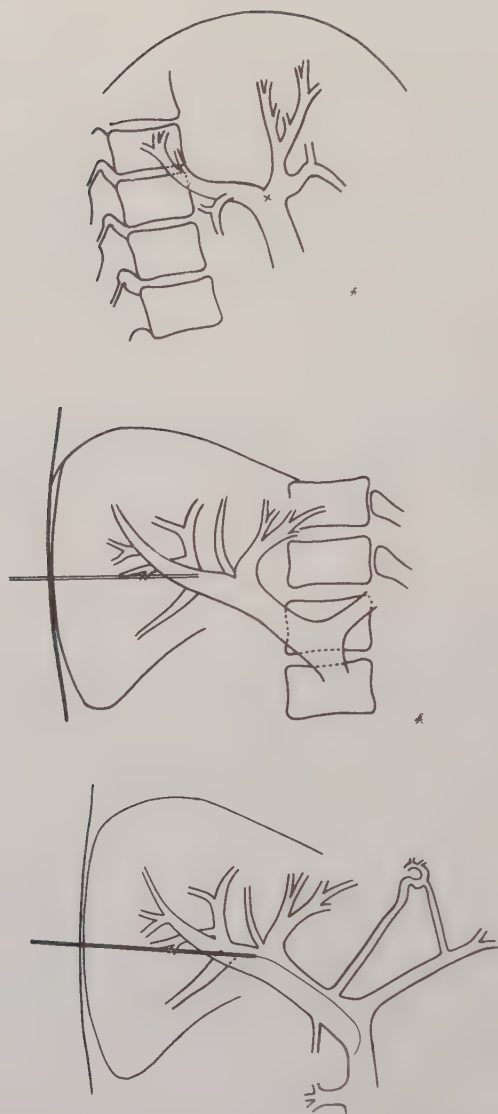


Fig. I. Aspects of the technique of percutaneous trans-hepatic portography.

- a) Relation of porta hepatis to vertebral bodies, as seen from the side
- b) Needle in good position in right branch of portal vein
- c) Guide wire advanced to upper part of superior mesenteric vein

vein; filling of the posterior superior pancreaticoduodenal vein (PSPD), of the upper and lower splenic hilus collaterals, a retroperitoneal plexus, the left renal vein, intercostal veins; the presence, if any, of segmental intrahepatic flow; the extent of collateral system and the presence of at least one "large" collateral. Clinical data extracted from the records were: number of gastrointestinal bleedings; magnitude of the last bleeding before the roentgen examination measured as the number of units of blood infused; serum albumin; serum bilirubin; platelet count; Normotest; APTT; degree of encephalopathy, as judged on clinical grounds, with EEG and with psychometric investigations; sex; age; duration and etiology of liver disease and presence, if any, of ascites. These variables were studied for intercorrelations with the aid of statistical methods described in a later section.

Chronic hepatic encephalopathy. A psychometrical study (II): Data, both prospective and retrospective collected from the hospital records, were obtained about the etiology of the cirrhosis, clinical evaluation of the encephalopathy and the results of conventional electroencephalopathy investigation. This investigation was the standard type used in our hospital and the results were classified as: A. clear-cut encephalopathy, B. suspect encephalopathy and C. no signs of encephalopathy.

The psychometric test battery used consisted of various tests selected to measure different intellectual and psychomotor functions. The first test was a synonym test designed to measure the patients verbal capacity. As shown in other investigations, this test also gives rough idea of the patient's premorbid intellectual capacity. The logical inductive test measures the general mental capacity: in this test the patient is shown 5 geometric figures and is requested to choose the one that differs in some particular way from the other 4 (Dureman 1971).

Also the block test measures general mental capacity. With the aid of blocks the patient tries to copy patterns of varying complexity (Dureman 1971). The word pair test is sensitive for revealing disturbances of memory: in this test the examiner reads 10 pairs of words. The subject is afterwards given the first word of each pair and requested to say the second from memory. This is repeated three times with different sets of words each time (Cronholm 1954).

Appreciation of form and memory of form was tested with the so-called memory for design test (MFD) and Benton's visual retention test. The patient is shown geometric figures which he is afterwards requested to reproduce from memory. Benton's test uses simpler figures than the MFD test and tests mainly memory.

The colour word test assesses cognitive flexibility: the patient is requested to name the colour of the print of 100 names of colour where the colour of the print does not correspond to the word (Smith 1972). The reaction time was measured in a simple and multi-choice situation.

The results of all the test except of MFD and the Benton test, were transformed to an age-adjusted so-called Stanine-scale with 9 steps from 1 to 9 with an average of 5 and standard deviation of 2.

Neurotransmitter changes in the rat brain following portacaval anastomosis (III): Portacaval anastomosis was done according to the method described by Lee and Fisher (1961). The animals were sacrificed by decapitation under light ether anesthesia 6 weeks after the shunt and the brain was removed immediately, the olfactory bulbs were removed and in some parts of the experiment the brains were dissected into three parts, viz the telencephalon, the diencephalon and the brain stem (Fig.II). The cerebellum and the pineal body were discarded.

5-hydroxytryptamine was determined fluorometrically according to Bertler (1961). Noradrenalin and dopamine were determined with Häggendahl's (1963) modification of the method described by Bertler, Karlsson, Rosengren and Waldeck (1958).

Treatment with L-dopa: The animals treated with L-dopa were given 1.5 mg per 100 g bodyweight intraperitoneally every day seven days before they were sacrificed.

Protein loading: 10 ml fresh rabbit blood was given via a feeding tube 5 hours before sacrifice.

Incubation with ^3H -tryptophan in vitro: Thin sections of cortex were incubated with ^3H -tryptophan for 30 minutes. The incubate was then homogenised in acetic acid. Carrier substances, which were not labelled, were added to the homogenate and drops of part of the supernatant were deposited on thin layer plates of silicon gel. 5-HT and 5-HIAA were chromatographically separated from other metabolites, scraped off the plates and mixed with water. The recovery of 5-HT was 50%, that of 5-HIAA, 80%. ^3H -tryptophan was separated from indole acids by passing

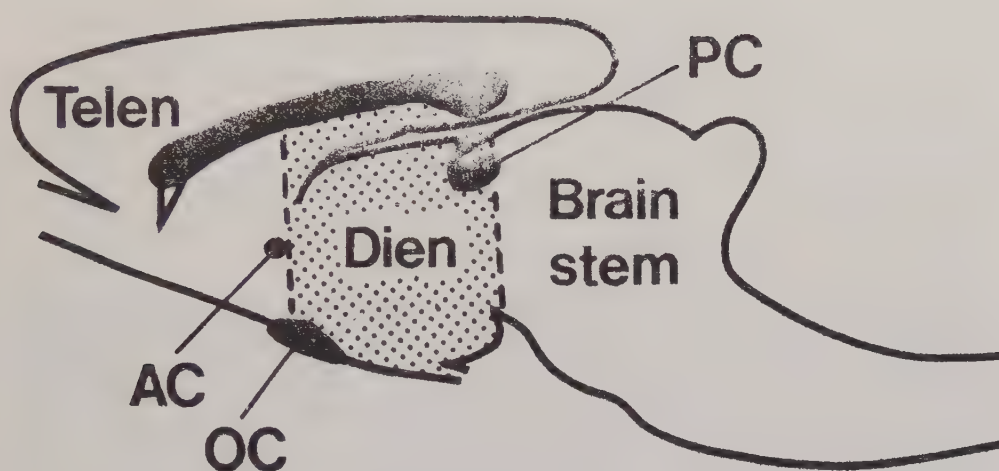


Fig. II. Brain dissection procedure.

Telen = Telencephalon

Dien = Diencephalon

Ac = Anterior commissure

Pc = Posterior commissure

Oc = Optic chiasma

the medium through Sephadex G-10 columns. The eluate containing the indole acids was freeze-dried and the residue was removed with sodium acetate. 5-HIAA was separated from other indole acids by thin-layer chromatography. The recovery of 5-HIAA was 100%. The values obtained were corrected for recovery. The blank values were obtained by using identical tissue that was boiled before being incubated. The method has been described in detail by Björklund, Axelsson and Falk (1976).

Some factors predicting survival after portacaval shunt (IV): Information about the following variables were extracted from the hospital records of the 134 cases: sex, heart disease, alcoholism, ascites, oedema, serum protein, serum albumin, serum globulin, alkaline phosphatases, serum bilirubin, bromsulphthalein retention, portal pressure before and after establishment of shunt, fall in portal pressure after establishment of shunt, date of operation, date of death or duration of survival at the end of the study. The data obtained were processed in a Hewlett-Packard 9830 minicomputer. With the aid of a specially designed programme the values of the variables were distributed among two or three classes and the survival at the three predetermined intervals of 1 month, 1 year and 5 years was calculated.

Results of a modified distal splenorenal shunt for portal hypertension (V): The principle of the operation is apparent from Fig. III. The splenic vein was divided, and the distal part was anastomosed end-to-side with the left renal vein. Unlike Warren's original operation (Warren et al 1969), the coronary vein was not ligated close to the portal vein. Neither was the right gastroepiploic vein. Instead the paraoesophageal veins were ligated near the coronary vein or the coronary vein near the cardia.

The patients were followed up 3 months after the operation and then at least once a year. Coeliac arteriography and superior mesenteric arteriography were done preoperatively, soon after the operation and in many cases 6 months and 1 year after the operation and in some cases also annually. Roentgen examination of the stomach and oesophagus was done at each follow-up, as was electroencephalography and in some cases also psychometric tests for detection of encephalopathy.

Statistical methods

In Part I several statistical methods were used. The choice of the methods varied according to the scale with

FIG 3

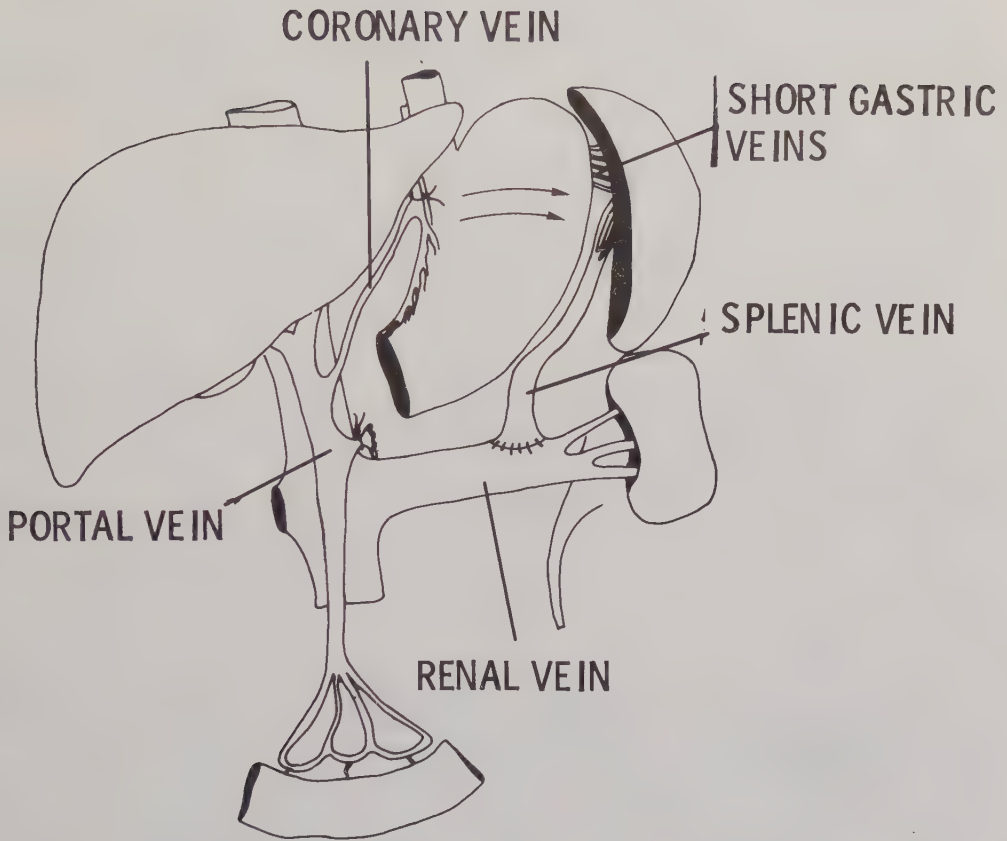


Fig. III. Our modification of the distal splenorenal shunt. Observe site of ligation of para-oesophageal veins.

which the data were to be measured or converted to. The three main scales are the nominal scale, rank scale and the interval scale. When both variables were on the nominal scale the χ^2 test or Fisher's exact test was used. When both values were on the rank scale, Spearman's test was used. When both were on the interval scale, we used linear regression. When one of the variables was found on the nominal scale and the other on the rank scale, Kruskal-Wallis test was used and as a special case of this Mann-Whitney's U-test. When one of the variables was on the nominal scale and the other on the interval scale, we used the analysis of variance (ANOVA). As a special case of ANOVA we used Student's t-test. To check whether results on interval test scale could be fitted to a normal distribution, it was tested with Kolmogorov-Smirnoff-test and the probit paper test. If normal distribution criteria were not fulfilled the data were transformed to a rank scale. In this part, as in the other parts, $p < 0.05$ was accepted as the lowest level of probability.

In Part II the results of the tests were on a special interval scale a so-called Stanine scale. Differences between group mean values were tested with Student's t-test. In comparisons between the results of the psychometric test, EEG and clinical evaluation, a simple sign test was used, which assumes that the data are on a nominal scale.

In Part III all data were on an interval scale and for comparison between the group means Student's t-test was used.

The purpose of the multiple linear regression used in Part IV was to find the best linear relation between the dependent variable and all the independent variables. This corresponds to mathematical calculation of the plane with $n-1$ dimensions in a space with n dimensions that was closest to all the data. The technique used in this investigation is a so-called backward regression i.e. a model with all the independent variables was constructed first. For each variable a F-test was performed to check whether the regression coefficient differed significantly from 0. The variable with the smallest F-value was then excluded and a new model was constructed with the remaining variables. This procedure was repeated until all the variables had a F-value exceeding the critical level of $p = 0.05$.

In Part V use was made of Wilcoxon's test which corresponds to Mann-Whitney's U-test but for paired data. It was used after conversion of the data from the interval scale

to the rank scale because of the uncertainty of the criterion for a normal distribution. Further, for the same reason Spearman's R-test was used on one occasion. Fisher's exact test was used for comparisons between two proportions.

All these statistical tests are described in most statistical handbooks. As for the multiple linear regression, see, for example, Snedecor-Cochran (1965) and for an exhaustive analysis of the test in medical studies, see Björn Andersen (1971). The non-parametric tests, i.e. rank sum test and tests with data in the nominal scale are described in detail in Siegel (1956).

RESULTS

Correlation between percutaneous transhepatic portography and clinical findings in 56 patients with portal hypertension (I): In most cases several collaterals were demonstrated. A spontaneous shunt to the left renal vein was seen in 37% (95% confidence interval 24-51%), the umbilical vein in 30% (18-44%), a retroperitoneal plexus in 39% (26-53%) and collateral flow via oesophageal varices in 85% (73-93%).

Hepatofugal flow in the main portal vein was demonstrated in 7 of 54 cases and segmental hepatofugal flow in an intrahepatic branch in 4 of 54 cases.

The number and severity of the gastrointestinal haemorrhages was found to be correlated only with the hepatofugal flow through the portal vein. In the presence of such a flow the gastrointestinal haemorrhages were significantly more severe. Otherwise, no significant correlations could be found between the severity of the haemorrhages and the estimated size of the varices.

The portal pressure was not significantly correlated with any of patterns of the collaterals except that patients with hepatofugal flow had a somewhat higher portal pressure than those with a hepatopetal flow (38 ± 6 cm H₂O against 33 ± 6 cm H₂O).

No correlation could be demonstrated between the portal pressure and the severity or number of gastrointestinal haemorrhages.

Some factors influencing the severity and number of the gastrointestinal bleedings could be recognised. Patients

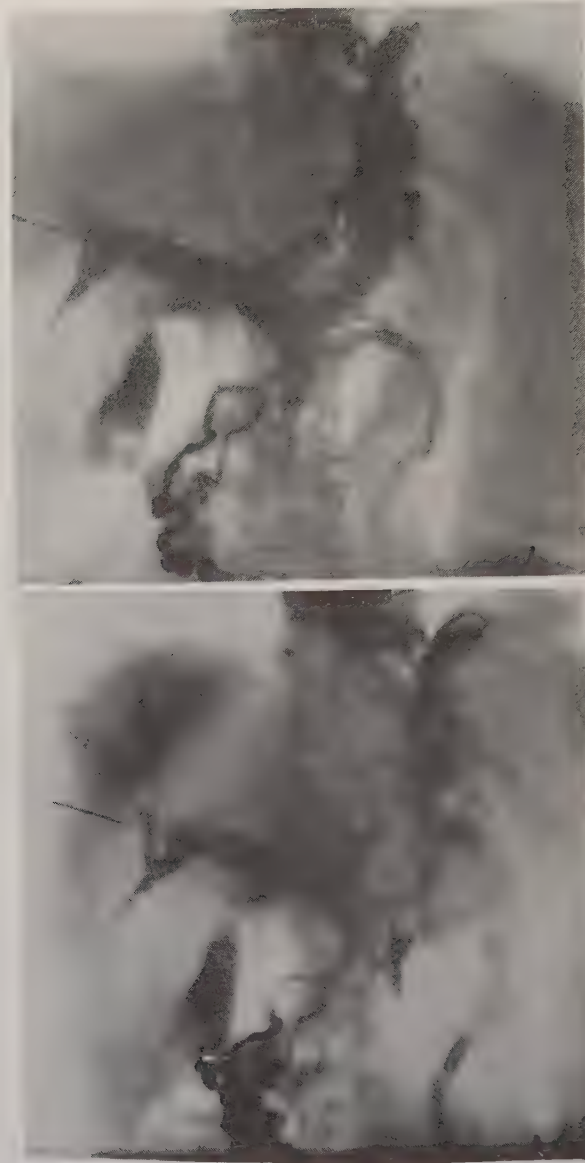


Fig. IV. Extensive collaterals in portal hypertension. a) Early portographic phase. Retrograde flow through coronary vein, oesophageal varices, posterior superior pancreaticoduodenal vein and inferior mesenteric vein. b) Late portographic phase. Large retroperitoneal plexus.

with alcoholic cirrhosis had significantly more severe haemorrhage than patients with other forms of cirrhosis. The number of episodes of haemorrhage was correlated with the platelet counts mainly because patients without such bleeding had a higher platelet count than those who had had bleeding of the upper alimentary tract.

The pattern of the collaterals did not vary with liver function or portal pressure. Hepatofugal flow was significantly associated with an increased severity of encephalopathy.

Chronic hepatic encephalopathy. A psychometrical study (II): The patients were grouped according to the severity or absence of electroencephalographic evidence of encephalopathy into three groups, viz. clear cut encephalopathy, suspected encephalopathy and no evidence of the condition. Comparison of the groups showed that the verbal capacity, measured with the synonym test, was fairly good in all the groups and without any certain tendency to be lower in the group with frank encephalopathy. The other tests showed clearly poorer values for the patients with clear cut encephalopathy. Most tests also revealed a difference between the groups with and without suspected encephalopathy. Only two tests, however, viz. the block test and the word pair test, revealed any difference between the group with suspect encephalopathy and the one with a firm diagnosis of the condition.

EEG classified more patients as having suspect or clear cut encephalopathy than did clinical examination and the psychometric tests identified more such cases than did EEG. Only the difference between the psychometric and the clinical classification was significant.

No significant difference was found between the patients with a firm diagnosis of alcoholic and non-alcoholic cirrhosis. Nor was any such difference found between the patients with and without surgical portosystemic shunts. Most of the tests gave better results for alcoholics without cirrhosis than for those with non-alcoholic cirrhosis and those with alcoholic cirrhosis.

Neurotransmitter changes in rat brain following portacaval anastomosis (III): The concentration of serotonin in the brain six weeks after establishment of a portacaval shunt was about 30% higher than before the operation. The increase varied somewhat from one part to another (28% in the telencephalon, 20% in the diencephalon, and 35% in the brain stem). The noradrenalin increased 10-15% in all the regions but this increase was statistically significant only in the brain stem. The concentration of

dopamine varied but little and insignificantly.

The postoperative increase in the concentration of serotonin was completely reversed to normal by treatment with L-dopa, which had no demonstrable effect on the concentrations of noradrenalin and dopamine.

On comparison between the formation of 5-HT and 5-HIAA from radioactive tryptophan in vitro it was found that the total amount of 5-HT and 5-HIAA formed was the same in rats with a portacaval shunt as that in the control rats. But in the operated animals the proportion of radioactivity in the form of in the 5-HT formed was much smaller, and that in form of the degradation product 5-HIAA much larger than in the control rats. In the operated animals the amount of 5-HT formed was only 65% of that in the controls.

Protein loading with 10 ml fresh rabbit blood suppressed the serotonin concentration and the noradrenalin concentration in the portacaval shunted rats to the levels in the shamoperated controls. However, the protein load did tend to lower the neurotransmitter concentrations in the shamoperated group, though the difference was significant only for dopamine.

Some factors predicting survival after portacaval shunt (IV): Only two parameters contributed significantly to the multiple correlation coefficient in prediction of survival 1 month after the operation. The two parameters were the serum bilirubin and ascites. The significant multiple correlation coefficient which was found was 0.26, which corresponds to an explained part of the variation in death rate of 7%. The survival rate after 1 month was 90%.

The 1-year survival rate was 75%. Six parameters contributed significantly to the multiple correlation coefficient. They were, in descending order of importance; serum albumin, sex, serum bilirubin, bromsulphthalein retention, heart disease and ascites. The multiple coefficient was 0.55, which explains 30% of the variation of the death rate.

The 5-year survival rate was 41%. The factors contributing to the multiple correlation coefficient were: serum albumin, alkaline phosphatases, alcoholism and serum globulin. The significant correlation coefficient was 0.41, which explains 17% of the variation of the number of deaths.

Results of modified distal splenorenal shunt for portal hypertension (V): Of the 25 patients operated upon, 4 died within one month of the operation. One of the deaths was due to a technical surgical error. The shunt was occluded at autopsy. A further shunt became occluded within one month after the operation. No other occluded shunts were found.

Of 21 patients who survived the operation, bleeding recurred in 6, including the one with the occluded shunt. None of the patients died from such bleeding.

By 3 months after the operation the roentgenographic size of the varices had diminished in 6 of 17 patients. In 6 the varices were no longer demonstrable and in 5 they were unchanged.

Of the 20 cases that could be evaluated, death occurred in 10 within the period covered by the investigation (29 - 65 months, median time 43 months). Hepatic failure was the direct cause of death in 5 of these 10 and a contributory factor in a further 3.

Of the 9 patients still being followed up at the end of the investigation, only 2 had no manifestations of encephalopathy. Twelve patients with a distal splenorenal shunt were compared psychometrically with 13 with a portacaval shunt. No statistical difference in the results of the tests was found between the two groups.

The pressure in the portal vein did not change significantly after establishing the anastomosis. Comparisons of the pre- and postoperative angiograms showed a rapid decrease in the perfusion of the liver via the portal vein. A change from hepatopetal to hepatofugal flow in the portal vein was noticed in 6 of 16 cases. Post-operatively the blood flowed mainly via the coronary vein, through tortuous veins in the fundus to the splenic vein and the shunt (see Figs. V a and b).

After the operation the preoperatively enlarged spleens diminished in size, but pre- and postoperative platelet count did not suggest any change in the hypersplenism.

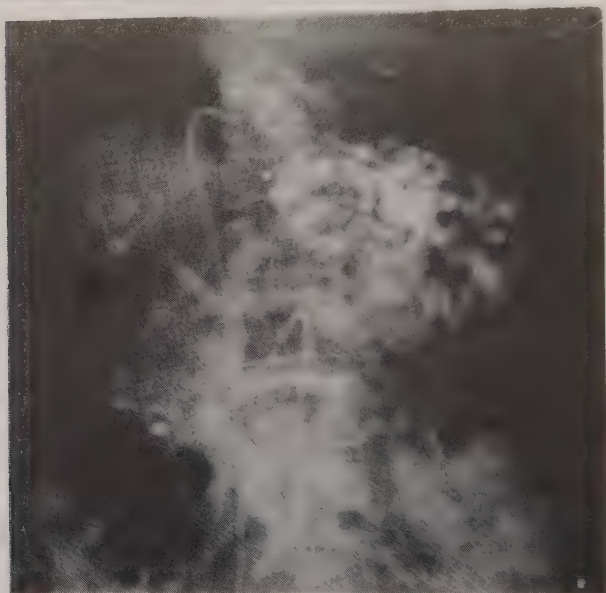


Fig. V. Distal splenorenal shunt. Venous phase of sup. mes. arteriography.
 a) Preoperatively
 b) One month after operation
 Reduction in hepatic portal perfusion and deviation of venous flow towards the area of the shunt.

DISCUSSION

What can be done to improve the prognosis of portal hypertension? Liver cirrhosis claims more than 800 deaths a year in Sweden (Central Bureau of Statistics, Stockholm 1976). Most of these deaths are caused by complications of portal hypertension. Also the quality of life of patients with this disease is reduced by the effect of the liver disease on their general condition, by ascites and by encephalopathy and the impending risk of life-threatening haemorrhage. The clinical importance of the problems created by the condition are therefore obvious.

Though questions, mainly social and medicosocial, bearing on the prophylaxis of the disease lie beyond the scope of the present investigation, it might not be out of place to mention that even if alcoholic cirrhosis could be entirely eliminated, it would not mean the disappearance of portal hypertension. Between one third and half of the patients in our material had cirrhosis of some origin other than alcoholism.

The development of collaterals in portal hypertension is associated with at least the two most dreaded complications, viz. chronic, hepatic encephalopathy (Summerskill et al 1956) and the risk of recurrent bleeding from the upper alimentary tract. In Part I we examined the development of collaterals with the aid of percutaneous transhepatic portography and found that most of the patients had a large number of collaterals for the outflow of blood from the liver. The number and size of such collaterals did not vary with sex, etiology of the liver disease or liver function. The main collaterals visualized at our examination can also be demonstrated in the absence of portal hypertension (Thamm 1940). The view that the development of a collateral circulation in caudal direction should be capable of preventing the development of oesophageal varices (Jackson 1963, Hassab 1967) could not be confirmed in our investigation. Neither could be demonstrate any large collaterals capable of coping with the entire collateral flow (Wexler et MacLean 1975).

The only tentative conclusion one might draw from our finding is that the development of collaterals in portal hypertension is a mainly passive process and that the

selection of collaterals that develop will probably depend chiefly on the possibility of the existing communications between the portal and caval system to dilate and the resistance to the portal flow through the liver.

Hepatic failure combined with portosystemic shunts causes neurological symptoms in the CNS and in the periphery. Hepatic neuropathy has been described by, among others, Knill-Jones et al (1972) and Kardel et al (1974). But it is rarely so severe as to cause the patient any appreciable inconvenience (Kardel 1976). Disturbances of the CNS are much more troublesome for the patient. The symptoms are essentially a varying suppression of the level of wakefulness; motor symptoms, such as tremor, asterixis, increased muscle tone; and various other symptoms such as hyperventilation, dysarthria, disturbances of sleep and blunting of the intellect. Loss of consciousness and the motor symptoms are well known and easy to diagnose. But intellectual blunting is not. In Part II psychometric tests showed that 28 out of 40 patients with portal hypertension had suffered a suppression of their intellectual level. Similar observations have been made by other workers (Zeegen et al 1970, Kardel et al 1970). Comparison of the results of the psychometric tests revealed that tests measuring mental adjustment and verbal memory and to some extent the reaction time, were the ones that best reflected the intellectual blunting. On the other hand, the verbal capacity, as measured by the ability to find synonyms for a given word, was well preserved even in patients with considerable reduction of their intellect or striking EEG changes. This explains why it sometimes proved so difficult to detect such changes at ordinary clinical examination and at the taking of the patient's history. Many patients without any electroencephalographic abnormalities or clinical findings had suffered clear reduction of their intellect.

Germain et al (1973) showed that treatment with lactulose improved the intellectual capacity of patients with alcoholic cirrhosis and encephalopathy, though the patients themselves did not notice the improvement. Should further investigations corroborate such improvement, it would mean that efforts should be made to detect any intellectual impairment even in patients without other manifestations of encephalopathy and treat the condition.

The intellectual capacity was not found to vary with the origin of the cirrhosis, i.e. alcoholic or other etiology. The blunting of the mind seen in alcoholics and due to a direct toxic effect on the brain (Claesson and Karlsson 1970)

is thus apparently not discernible in a group of patients with such blunting due to hepatic encephalopathy. This assumption is strengthened also by the comparison with a group of men without cirrhosis but with confirmed alcoholism, results of the test were always better than in the two groups with cirrhosis.

In a prospective randomised comparison between patients with and without a portacaval shunt Mutchnick et al (1974) found that portosystemic encephalopathy had occurred in 20% of the patients before they had been included in the study and during the study 35% of the controls and 53% of the patients with a shunt had developed encephalopathy within a follow-up period of 4 years. This difference was not significant. Severe (defined as spontaneous recurrent episodes of coma) chronic portosystemic encephalopathy was diagnosed in 20% of the group with a shunt and in 3% of the other group. This difference was statistically significant. Establishment of a portacaval shunt could thus aggravate portosystemic encephalopathy defined as episodes of low level of wakefulness. Whether the mental capacity is affected by a portal shunt is still debatable. Kardel et al (1970) found no significant differences in the psychometric tests performed before and after establishment of a portacaval shunt. Neither did we find any noteworthy difference between a group of patients with surgically created portosystemic anastomosis and a group without shunts. Thus, judging from the few observations made, a portosystemic shunt does not appreciably influence the patient's mental capacity.

The pathogenesis of hepatic encephalopathy has received much space in the literature. The cause of the condition has long been regarded as the hyperammonemia accompanying liver cirrhosis with portal hypertension and increasing with the consumption of meat. But no conclusive evidence of the role played by ammonia has so far been produced. Theories assuming that the ammonia interferes with the brain metabolism have been proposed. There are essentially two possibilities of such interference viz. that the ammonia causes the formation of a toxic substance or that ammonia causes a decrease of one or more essential substances with a "deficiency" condition as a result. The most widely known theory is the one suggested by Bessman and Bessman (1955). Ammonia-binding processes lower the concentration of alpha-ketoglutarate in the brain according to the formula $\alpha\text{-ketoglutarate} + \text{NH}_3 \longrightarrow \text{glutamate} + \text{NH}_3 \longrightarrow \text{glutamine}$. Alpha-ketoglutarate is one of the steps in the citric acid cycle and the binding of ammonia is therefore thought to inhibit the turnover of energy in the brain. But despite extensive investigations with

exposure to ammonia (Hindfeldt 1972, 1974), hepatectomy (Siesjö et al 1971) or portacaval anastomosis (Holmin 1973) so far it has not been possible to demonstrate any reduction in the energy turnover in the brain.

Since these investigations could not produce corroborative evidence for Bessman's theory that hepatic encephalopathy is due to a disturbed turnover of energy in the brain it was suggested that the condition might instead be due not to "power failure", but to "transmission failure" instead. In other words, one imagined the possibility of disturbed transmission in the various connection between the nerves. Walker et al (1971) studied the content of different neurotransmitters in the brain in hyperammonemic coma, but found no changes. It would seem that ammonia per se does not affect the content of neurotransmitters.

Fischer and Baldessarini (Fischer 1974) proposed a theory of the origin of transmission failure, because of the formation of false neurotransmitters in liver disease. According to this theory, false transmitters, beta-hydroxylated phenylethylamines (of which octopamine is best known) successfully compete with the ordinary neurotransmitters, mainly noradrenalin, in the synapses in the central and peripheral systems. Octopamine has also been found in increased concentration in the blood and urine from patients in hepatic coma (Fischer et al 1972). At any rate, the experimental evidence for a reduction of the noradrenalin content in the CNS in hepatic encephalopathy is fairly meagre. But Dodsworth et al (1974) found a definitely low concentration of noradrenalin in the brain of rats in which a portacaval shunt had been created and in which the hepatic artery had later been ligated. In our investigation (III) on rats we found that a portacaval shunt was followed by a moderate increase in the concentration of noradrenalin in the brain. This does not lend support to the assumption that deficiency of noradrenalin is the most important cause of hepatic encephalopathy. Whether false transmitters play a role in the pathogenesis of hepatic encephalopathy is still an open question.

Another interesting possibility of the mechanism responsible for the development of cerebral changes in hepatic encephalopathy is the one envisaged by Fischer et al (1975). In human beings with liver cirrhosis and in animals with liver damage, mainly in the form of a portacaval shunt, characteristic changes occur in the amino acid pattern in the blood (Iber et al 1957, Iob et al 1966, Aguirre et al 1974). The content of amino acids with branched chains i.e. valine leucin and isoleucin seems to be diminished

while that of the aromatic amino acids, tyrosine and phenylalanine is increased. These neutral amino acids are probably the ones competing with tryptophan for a common transport mechanism across the blood-brain barrier (Fernstrom and Wurtman 1972). These changes in the amino acid pattern thus seem to raise the level of the tryptophan in the brain as a consequence of that increase the concentration of serotonin. We also found (III) a moderate increase in the serotonin concentration in the rat after establishment of a portacaval shunt in the rat. The increase in the serotonin content was demonstrated in the telecephalon in the diencephalon and in the brain stem, where most of the central serotonin neurons have their cell bodies.

Low dosage L-dopa treatment normalized the serotonin levels, that were raised by the portacaval shunt, which is noteworthy since there is evidence that L-dopa can reverse hepatic coma (Abramsky and Goldschmidt 1972, Fischer et al 1976). Our observation (III) that the synthesis of serotonin from tryptophan decreased by 35%, while the rate of formation of 5-HIAA from serotonin increased by about 60% after establishment of a portacaval shunt also indicated a change in the activity in the serotonin neuron caused by this operation on the rat. How these changes in the serotonin neuron should be able to bring about the clinical picture of hepatic encephalopathy is still a matter of conjecture.

One might imagine that disturbances of the amino acid pattern in the blood can affect the synthesis of other neurotransmitters. Tyrosine, which is a normal precursor of the catecholamines, but in the event of accumulation of tyrosine which can be seen in rats with portacaval shunt (James 1976), it appears to be used mainly in the synthesis of octopamine (Fischer 1976). This substance might be able to act as a false neurotransmitter in noradrenergic neurons, or should decreased synthesis of noradrenalin explain the encephalopathy. But the evidence for a decrease in the concentration of noradrenalin in hepatic coma is meagre, and in rats with a portacaval shunt the noradrenalin level is, if anything, raised.

Changes in the amino acid pattern in the blood and caused by protein loading is the probable explanation of the changes in the neurotransmitters in the rats (III) in which fresh blood was given directly into stomach. That the serotonin level returned to normal after protein loading in rats with a portacaval shunt does not, however, lend support to the theory that the changes in the concentration of serotonin are the cause of hepatic encephalopathy.

An argument in favour of the amino acid induced changes in the transmitter substances being the cause of hepatic encephalopathy, however, is the observation that normalization of the plasma amino acids by intravenous administration of amino acid solutions is probably associated with a longer survival of dogs with a portacaval shunt (Fischer et al 1975) and a possible regression of hepatic encephalopathy in man (Fischer et al 1976).

At present this theory appears to be the one giving the best hope for progress in the investigation of the pathogenesis of hepatic encephalopathy and the search for better methods of treatment of the condition. At present the long known treatment with lactulose, intestinal sterilization with broad spectrum antibiotics and restriction of dietary protein still maintains its position. The therapeutic value of L-dopa is not yet certain.

The problem is still more complex in the care of patients with existing, or the risk of developing, the most important complication of portal hypertension, viz. bleeding from the upper alimentary tract.

As mentioned in the introduction, only relatively few of the patients with oesophageal varices develop gastrointestinal haemorrhage. In Baker's (Baker et al 1959) study the frequency of this complication was 28.6% and similar figures have been given by Conn et al (1972), for example. According to the last-mentioned authors, ascites practically always preceded bleeding from the oesophageal varices, but otherwise they found nothing that could "reveal any clinical, laboratory, radiologic or endoscopic feature that would permit prospective recognition of those patients destined to bleed from oesophageal varices".

In our 56 patients with portal hypertension and examined with percutaneous transhepatic portography (I) also the bleeding pattern was studied for any correlation with the roentgen findings. The comparison was retrospective, and the bleeding pattern was influenced by several factors difficult to control, for which reason the analysis was of somewhat limited value. We did, however, find that hepatofugal flow was associated with profuse haemorrhages. But otherwise we found no association between the angiographic signs and the bleeding pattern. Thus, neither the estimated flow through the varices nor the portal pressure were of any value for predicting the chances of bleeding from oesophageal varices. Neither could we corroborate the conclusion by Jackson (1963) and Hassab (1967) that patients with "cephalic" collaterals in the

splenoportogram are more often destined to bleed from varices than are those with "caudal" collaterals. However, other features might perhaps prove useful in the prediction of oesophageal bleeding in patients with portal hypertension. In our investigation we found that patients with alcoholic cirrhosis bled more profusely than those with cirrhosis of some other origin and, second, in patients with only a single bleeding or no bleeding the platelet count was much higher than in those with recurrent haemorrhage. However, since our investigation was retrospective, caution should be exercised in the evaluation of these findings, which preferably should be regarded as the basis for further prospective investigations. Another path that might be worth pursuing is suggested by Dagradi's (1972) observation that the risk of bleeding varies closely correlates with the endoscopic size of the varices. This is not in accord with our findings in the PTP investigation. However, the two investigation methods will probably not measure the same thing because in PTP it is mainly the flow through the varices that is estimated, while in the endoscopic investigation it is the size of the varices. Moreover, the criteria for including patients in the two studies were quite different.

During the last 25 years preventive treatment of recurrent oesophageal bleeding has consisted essentially of establishment of a portacaval shunt. The method was introduced without any proceeding well controlled trials and proved very effective for warding off recurrent haemorrhage. It therefore very soon became popular and remained so until its values was questioned by controlled investigations. That it did not prolong the life of patients with varices but without bleeding (Jackson et al 1968, Resnick et al 1969, Conn et al 1972) could be explained by the fact that in this situation many patients were operated upon unnecessarily, i.e. patients in whom oesophageal bleeding would never have occurred even if they had not been operated upon. However, three controlled prospective studies of the value of the therapeutic shunt, i.e. shunt established after the patient had bled at least once (Jackson et al 1971, Resnick et al 1974, Rueff et al 1976) revealed no significant difference in survival between the groups with and without a shunt. This appears to argue strongly for abandonment of the use of portacaval shunt in portal hypertension, but the above mentioned investigations were very difficult to carry out and their findings are hardly really conclusive. For example, in the investigation by Rueff et al 18 of the 49 patients in the control group underwent establishment of an emergency portacaval shunt because of uncontrollable bleeding during the follow-up period. The investigation appears to

be a comparison between portacaval shunt immediately after the first gastrointestinal bleeding, on one hand, and postponing the portacaval shunt until mandatory because of life-threatening haemorrhage on the other, rather than between a group treated with a shunt and a group treated given only medicinal treatment. In the investigation by Resnick et al the groups were so small that the difference between end-to-side shunt group and the group given only medicinal treatment was $20\% \pm 28\%$, i.e. the "true" difference were with probability 95% between plus 48% and minus 8%. In their material then it is most probable that the portacaval shunt was associated with a longer survival, though the difference was not significant.

It is, however, obvious that better methods are necessary to improve the prevention of recurrent gastrointestinal bleeding. This goal may be approached along three different pathways, one aiming at a better selection of patients for portosystemic shunt; one, at technically improved portosystemic shunts; and one, at developing methods not including portosystemic shunts.

In efforts to improve the prognosis after portacaval shunt interest has been focused on various preoperative factors and their effect on survival of patients subjected to such an operation. The predictive value of liver function criteria according to Child is well established. Other liver function tests, such as bromsulphthalein retention (Hsu 1972, Turner et al 1974), have also been described as useful in the prognosis quoad vitam. Inclusion of further clinical features over and above the results of the liver function tests has not increased the reliability of the prognosis (Campbell et al 1973, Turcott and Lamberg 1973, Maillard et al 1974). Various haemodynamic variables have also been studied for any correlation with survival, in order to facilitate a better selection of patients for operation. But such endeavours have proved unsuccessful (Burchell 1974, Charters et al 1975). The only two features we found (IV) to be correlated with survival at one month were the serum bilirubin and the presence of ascites, either in the history or at the time of the operation. It should be stressed that our investigation only dealt with patients who had been operated upon electively with a portacaval shunt and therefore do not apply to patients who are subjected to emergency or semi-emergency operations. Our result is exactly the same as that reported by Malt et al (1976).

It would thus appear that Child's criteria for the prediction of the operative mortality are unnecessarily complex. The picture is quite different when predicting the 1-year survival when four liver function tests, viz. serum albumin,

serum bilirubin, ascites and the bromsulphthalein retention, contribute substantially to the prediction of survival. Two other useful factors in this prediction were age and knowledge of heart disease, if any, in the patients' history. Here then the calculations are much more complex. But the calculation of the 5-year survival is based partly on other liver function tests, namely serum albumin, alkaline phosphatases, and serum globulin and moreover knowledge of the patient's habitual consumption of alcohol. The influence of the last mentioned factor is probably due to that the postoperative prognosis is much gloomier for patients who continue to drink (Foster et al 1971).

We found no correlation between peroperative measurements of the portal pressure and survival. Despite earlier observations, the findings by Burchell et al (1976) strongly suggest that measurement of certain haemodynamic factors might be useful in the selection of patients for portacaval shunt. It was found that the survival after establishment of a shunt was closely associated with the ability of the patient to increase the flow through the hepatic artery in response to portal occlusion.

Further development of the statistical model used in our investigation and including a large number of patients would allow more exact calculation of the chances of survival after operation with a portacaval shunt. However, if such calculations are to give the largest possible amount of information, corresponding calculations should be made for patients with portal hypertension and gastrointestinal bleeding but not operated upon with any shunt. Further criteria that should be included seems, at least for the time being, to be the above-mentioned measurement of the change in flow through the hepatic artery and some histologic criteria for hepatocellular damage (Mikkelsen 1974). These are probably the best possibility of contributing further to a more precise prediction.

The first portosystemic shunt used and regarded as a standard method was the end-to-side portacaval shunt. Numerous attempts have been made to improve the method. (For review, see for instance R. Malt 1976.) Judging from the literature, none of the modifications (e.g. side-to-side portacaval shunt, proximal splenorenal shunt and mesocaval H-shunt) have proved to be indisputably better than end-to-side portacaval shunt, except possibly in certain situations.

Selective drainage of the oesophageal varices with preservation of the portal perfusion could, theoretically,

reduce or prevent the increased frequency of deaths from hepatic failure after portacaval shunt. There are two forms of operations claimed by their inventors to have such an effect. One of them is a shunt between the coronary vein and the vena cava (Inokuchi et al 1975). This theoretically most interesting selective operation appears never to have been performed outside Japan. Of the 253 operations attempted there, 117 were actually performed. The results were good: practically no recurrent bleeding and no complications. The reason why the method has not been used more widely is probably to be sought in the fact that the operation is may be exceedingly difficult to perform.

The distal splenorenal shunt is another operation based on the same idea. The distal part of the divided splenic vein is anastomosed to the renal vein. The coronary vein, the gastroepiploic vein and other collaterals to the spleen are ligated. The aim is to conduct the blood from the oesophageal varices almost exclusively through the vena gastricae breves down to the splenic vein and out into the renal vein. Warren et al (1974) reported excellent uncontrolled results of the operation, and enthusiastic reports of a few cases followed up for only a short time have been reported by other workers (Jacquet 1974, Mosimann and Rausis 1974, Silver et al 1974, Thomford et al 1975). Mosimann and Loup (1977) have also reported their total experience with the operation (22 cases). They had more favourable results than ours in respect of re-bleeding, encephalopathy and long survival. The preoperative liver function in their series appeared to be better than in ours.

In our modification of the method, in which the coronary vein and the gastroepiploic vein were not divided, later angiography showed that the shunt could not be regarded as selective and that the portal perfusion often rapidly diminished. The same angiographic result was found by Nabseth et al (1975). The obvious result of decreased portal perfusion of the liver was that the frequency of encephalopathy was high and death from hepatic failure common. But the operation did substantially prevent the frequency of recurrent bleeding and of deaths from such re-bleeding. The reduction in the size of the varices was essentially the same as that reported by Warren et al (1974) but we could not corroborate their remarkable finding of a complete absence of bleeding from the upper alimentary tract. Whether the fairly moderate difference in operative technique between our methods and Warren's really can produce entirely different haemodynamic results must abide repeat angiography at follow up of patients operated upon with Warren's original method. It is difficult to imagine any substantial difference since it is hardly possible to

interrupt all venous communications between the main portal system and the system of the splenic vein besides which newly formed blood vessels in adhesions after operation can probably also be dilated and conduct more blood from the main portal system towards the shunt.

Theoretically, complete deviation of the frequently very large flow through the splenic vein by a distal spleno-renal shunt should diminish the perfusion of the liver after the operation. We sometimes observed a rapid decrease of the liver perfusion after distal splenorenal shunt and we feel that this argues in favour of the above theory, even though Warren et al (1974, 1976) had apparently not recorded such a phenomenon in their series. Warren et al (1976) recently published a randomised, controlled investigation of distal splenorenal shunt versus mesocaval H-shunt. That investigation clearly showed a smaller risk of the development of encephalopathy after the operation in cases with the selective shunt. Liver function, as measured by the maximal rate of synthesis of urea was also better in the groups with a distal splenorenal shunt. But the survival rate after the operation was the same in both groups. It would therefore appear that the decision whether the distal splenorenal shunt is superior to other shunts must abide the results of future prospective investigations.

Various methods not including a shunt have also been devised for the treatment of portal hypertension. They fall roughly into three groups. One aiming at removing varices or at stopping the flow through them; one, at reducing the amount of blood entering the portal circulation; and one aiming at facilitating spontaneous development of portosystemic collaterals. This classification is taken from Börjesson (1977), to which the reader is referred for a more detailed survey and discussion of the methods. The presentation of the evidence postulated to warrant their clinical application is anecdotic and randomised prospective studies are necessary if any of them is to find wider use.

Several of the methods, such as those using injection of sclerosing agents into the varices (Johnston and Rodgers 1973, Lunderquist and Vang 1974) seem to be suitable for such prospective investigations, which would probably be easier to arrange and realize than those using portosystemic shunts.

During the last decade emergency endoscopy is being more widely used to detect the source of bleeding in patients with haematemesis and melaena. In patients with known

varices, varying, but rather low, percentage of such haemorrhages have been found to emanate from the varices e.g. 0% (Borsari 1976), 18.5% (McCray et al 1969) and 38% (Waldram et al 1974).

If this criterion is included when selecting patients for operation barely any of all previous investigations will be relevant when predicting the result of treatment. This is because such investigations defined bleeding oesophageal varices in different ways, e.g. mainly as upper gastrointestinal bleeding with known varices and no ulceration or cancer found in roentgen examination.

This is true for all three above mentioned randomized clinical trials on therapeutic portacaval shunt as well as for the patients in our investigations.

An important task for future clinical investigations in the field of portal hypertension is to find out whether conventional therapeutic methods (such as portacaval shunt) will give different and perhaps better results in the group of patients where bleeding oesophageal varices are defined with the aid of examinations including acute endoscopy.

CONCLUSIONS

1. Extensive collaterals between the portal and caval systems are seen in most patients with portal hypertension. The collateralization is not correlated to liver function or portal pressure.
2. In portal hypertension percutaneous transhepatic portography appears to be of little help in identifying "high risk bleeders".
3. In portal hypertension thrombocytopenia and alcoholic cirrhosis are associated with a "high risk of bleeding".
4. Intellectual impairment is common in patients with liver cirrhosis with or without surgical portosystemic shunt even if routine clinical examination and EEG reveal nothing remarkable.
5. The most important cause of encephalopathy in cirrhosis and alcoholism seems to be the cirrhosis and not the direct effect of alcohol on the brain.
6. Changes in brain serotonin metabolism and brain serotonin neurons may help to explain hepatic encephalopathy.
7. Hospital mortality after portacaval shunt varies with the preoperative serum bilirubin and the presence or absence of ascites. When predicting 1-year and 5-year survival several other criteria not included in the Child classification have to be used.
8. A version of the distal splenorenal shunt without ligation of the coronary vein can be done with an acceptable risk of hospital mortality and with a probably reduced risk of death from rebleeding.
9. This version of the splenorenal shunt does not act as a selective shunt and carries a high risk of death from hepatic failure. The operation has probably no advantages over portacaval shunt.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to:

Assistant Professor Johannes Vang, my teacher, for the initiation of the study and for all his advice and guidance throughout this work.

Professor Stig Bengmark for the excellent possibilities for scientific work at his department and for his encouragement and special interest in my investigations.

My co-writers for their critical advice and all their other work.

Mr James L. Brown for the translation.

Mrs Gerda Seidel for skilful laboratory work.

Miss Gun Hansson for typing the manuscript.

Mr Ove Bengtsson for printing.

And finally my wife, Ingrid, not only for all her patience and encouragement, but also for typing many of the manuscripts.

REFERENCES

1. Abramsky, O., Goldschmidt, Z. Treatment and prevention of acute hepatic encephalopathy by intravenous laevodopa. *Surgery* 75:188, 1972.
2. Andersen, B. Praeoperativ vurdering af operativ risiko. F.A.D.L.'s Forlag A.S. Copenhagen 1971.
3. Aguirre, A., Yoshimura, N., Westman, T. et al. Plasma amino acids in dogs with two experimental forms of liver damage. *J. Surg. Res.* 16:339, 1974.
4. Baker, L., Smith, C., Lieberman, G. The natural history of esophageal varices. *Am. J. Med.* 26:228, 1959.
5. Bengmark, S. Surgical management of portal hypertension. In *Clinics in Gastroenterology* 4:2:395, 1975.
6. Benton, A.L. The revised visual retention test, Iowa City 1965.
7. Bertler, Å., Carlsson, A., Rosengren, E., Waldeck, B. A method for fluorimetric determinations of adrenaline, noradrenaline and dopamine in tissues. *Kungl. Fysiogr. Sällsk. Lund Förh.* 28:121, 1958.
8. Bertler, Å. Effect of reserpine on the storage of catecholamines in brain and other tissues. *Acta Physiol. Scand.* 51:75, 1961.
9. Borsari, G. Ösophagusvarizenruptur: Mythos oder Realität? *Z. Gastroenterol.* 41:235, 1976.
10. Bessman, S.P., Bessman, A.N. The cerebral and peripheral uptake of ammonia in liver disease with an hypothesis for the mechanisms of hepatic coma. *J. Clin. Invest.* 34:622, 1955.
11. Bismuth, H., Franco, D., Hepp, J. Portal-systemic shunt in hepatic cirrhosis. Does the type of shunt decisively influence the clinical result? *Ann. Surg.* 179:209, 1974.
12. Björklund, A., Axelsson, S., Falck, B. Intraneuronal indoleamines in the central nervous system. *Adv. Biochem. Psychopharm.* 15:87, 1976.

13. Blakemore, A.H., Lord, J.W.Jr. The technic of using vitallium tubes in establishing portacaval shunts for portal hypertension. *Ann. Surg.* 122:476, 1945.
14. Burchell, A.R., Moreno, A.H., Panke, W.F., Nealon, T.F.Jr. Hemodynamic variables and prognosis following porta caval shunts. *Surg. Gyn. Obstet.* 138:359, 1974.
15. Burchell, A.R., Moreno, A.H., Panke, W.F., Nealon, T.F. Jr. Hepatic artery flow improvement after portacaval shunt: A single hemodynamic clinical correlate. *Ann. Surg.* 184:289, 1976.
16. Börjesson, B. Subcutaneous transposition of the spleen. An experimental and clinical study. Thesis Lund, 1977.
17. Campbell, D.P., Parker, D.E., Anagnostopoulos, C.E. Survival prediction in portacaval shunts: A computerized statistical analysis. *Am. J. Surg.* 126:748, 1973.
18. Charters, A.C., Brown, B.N., Sviolka, S.C. et al. The influence of portal perfusion on the response to portacaval shunt. *Am. J. Surg.* 130:226, 1975.
19. Chiari, H. über die selbständige phlebitis obliterans der hauptstämme der Venae hepaticae als Todesursache. *Beitr. Path. Anat.* 26:1, 1899.
20. Child, C.G., Turcotte, J.G. The liver and portal hypertension, (chapter 1). W:B Saunders, Philadelphia, 1964.
21. Claesson, L.E., Carlsson, C.E. Cerebral dysfunction in alcoholics. A psychometric investigation. *Quart. J. Stud. Alcohol.* 31:317, 1970.
22. Conn, H.O., Lindenmuth, W.W., May, C.J., Ramsby, G.R. Prophylactic portacaval anastomosis - A tale of two studies. *Medicine* 51:27, 1972.
23. Crafoord, C., Frenckner, P. New surgical treatment of varicous veins of the oesophagus. *Acta Otolaryngol.* 27:422, 1939.
24. Cronholm, B., Melander, L. Memory disturbance after electroconvulsive therapy. I: Conditions six hours after electroshock treatment. *Acta Psychiat. Neurol. Scand.* 32:250, 1954.

25. Dagradi, A.E. The natural history of oesophageal varices in patients with alcoholic liver cirrhosis. An endoscopic and clinical study. *Am. J. Gastroenterol.* 57:520, 1972.
26. Denck, H., Sponer, D. Sklerosierung der Oesophagus-varicen. *Langenbecks arch. chir.* 342: 181, 1976.
27. Dodsworth, J.M., James, J.H., Cummings, M.C., Fischer, J.E. Depletion of brain norepinephrine in acute hepatic coma. *Surgery* 75:811, 1974.
28. Douglas, B.E., Snell, A.M. Portal cirrhosis. *Gastroenterology*, 15:407, 1950.
29. Drapanas, T. Interposition mesocaval shunt for treatment of portal hypertension. *Ann. Surg.* 176:435, 1972.
30. Dureman, J., Kebbon, L., Östberg, E. Manual till DS-batteriet. Skand. Testförlaget Stockholm 1971.
31. Fernstrom, J.D., Wurtman, R.J. Brain serotonin content: Physiological regulation by plasma neutral amino acids. *Science* 178:414, 1971.
32. Fischer, J.E., James, J.H., Baldessarini, R.J. Treatment of hepatic coma and hepatorenal syndrome: Mechanism of action of L-dopa and aramine. *Am. J. Surg.* 123:222, 1972.
33. Fischer, J.E. Hepatic coma in cirrhosis, portal hypertension and following portacaval shunt. *Arch. Surg.* 108:325, 1974.
34. Fischer, J.E., Funovics, J.M., Aguirre, A., James, J.H., Keane, J.M., Wesdorp, R.I.C., Yosimura, N., Westman, T. The role of plasma amino acids in hepatic encephalopathy. *Surgery* 78:276, 1975.
35. Fischer, J.E., Funovics, J.M., Falcao, H.A., Wesdorp, R.I.C. L-dopa in hepatic coma. *Ann. Surg.* 183:386, 1976.
36. Fischer, J.E., Rosen, H.M., Ebeid, A.M., James, J.H., Keane, J.M., Soeters, P.B. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. *Surgery* 80:17, 1976.
37. Foster, J.H., Ellison, L.H., Donovan, T.J., Anderson, A. Quantity and quality of survival after portosystemic shunts. *Am. J. Surg.* 121:490, 1971.

38. Galambos, J.T., Warren, W.D., Rudman, D., Smith, R.B., Salam, A.A. Selective and total shunts in the treatment of bleeding varices. *N. Engl. J. Med.* 295:1089, 1976.
39. Germain, L., Frexinos, J., Louis, A., Ribet, A. Etude en double aveugle du lactulose chez 18 malades atteints d'encephalopathie hépatique chronique après shunt port-cave. *Arch. Franc. Appar. Dig.* 62:293, 1973.
40. Gilbert, A., Weil, E. On the tension of the fluids of ascites. *Compt. Rend. Soc. Biol.* 51:511, 1899.
41. Gilbert, A., Villaret, M. Contribution to the study of the syndrom of portal hypertension. *Compt. Rend. Soc. Biol.* 60:280, 1906.
42. Gill, S.S., Eggleston, F.C., Singh, C.M. End-to-side splenorenal shunt for treatment of portal hypertension. *Arch. Surg.* 110:254, 1975.
43. Graham, F.K., Kendall, B.S. Memory-for-design; Revised general manual, *Percept. Mot. Skills.* 11:147, 1960.
44. Hallenbeck, G.A., Wollaeger, E.E., Adson, M.A., Gage, R.P. Results after portal-systemic shunts in 120 patients with cirrhosis of the liver. *Surg. Gynecol. Obstet.* 116:435, 1963.
45. Hassab, M.A. Gastrooesophageal decongestion and splenectomy in the treatment of oesophageal varices in bilharzial cirrhosis. Further studies with a report on 355 operations. *Surgery* 61:169, 1967.
46. Heller, A. Traumatic thrombosis of the portal vein. *Verhandl. Deutsch. Pathol. Gesellschaft* 7:182, 1904.
47. Hindfelt, B. Hyperammonemia and brain energy metabolism. Thesis Lund 1972.
48. Hindfelt, B. Acute hypercapnia and brain energy state in sustained hyperammonemia. *J. Neurochem.* 23:17, 1974.
49. Hoevels, J., Lunderquist, A., Tylén, U. Percutaneous transhepatic portography. To be published in *Radiology*.
50. Holmin, T. Portakaval shunt och hjärnans energitillstånd. Thesis, Lund 1973.

51. Hsu, K.Y. Portal systemic shunt for portal hypertension: Importance of bromsulphthalein retention for prediction of survival. *Ann. Surg.* 175:569, 1972.
52. Hurwitt, E.S., Altman, S.F., Gerst, G.R., Weber, B.M. Gastrointestinal bleeding due to splenic vein obstruction by pancreatic tumours. *Arch. Surg.* 68:7, 1954.
53. Häggendal, J. An improved method for fluorometric determination of small amounts of adrenaline and nor-adrenaline in plasma and tissues. *Acta Physiol. Scand.* 59:242, 1963.
54. Hästbacka, J. Thoracic transposition of the spleen for portal hypertension. *Annales Chir. et Gyn. Fennae* 60 supplement 176 (1-77) 1971.
55. Iber, F., Rosen, H., Levenson, S.M. et al. The plasma amino acids in patients with liver failure. *J. Clin. Lab. Med.* 50:417, 1957.
56. Inokuchi, K., Kobayashi, M., Ogawa, Y., Saku, M., Iwaki, A. Late results of a left gastric venous-caval shunt for esophageal varices. Analysis of 100 clinical cases. *Surgery* 78:628, 1975.
57. Iob, V., Coon, W.W., Sloan, M. Altered clearance of free amino acids from plasma of patients with cirrhosis of the liver. *J. Surg. Res.* 6:233, 1966.
58. Jackson, F.C., Perrin, E.B., Felix, W.R., Smith, T. Clinical investigation of the portacaval shunt: V Survival analysis of the therapeutic operation. *Ann. Surg.* 174:672, 1971.
59. Jackson, F.C. "Directional" flow patterns in portal hypertension. *Arch. Surg.* 87:307, 1963.
60. Jackson, F.C., Perrin, E.B., Smith, A.G., Dagradi, A.E., Nadal, H.M. A clinical investigation of the portacaval shunt II. Survival analysis of the prophylactic operation. *Am. J. Surg.* 115:22, 1968.
61. Jacquet, N. L'anastomose spléno-rénale distale dans le traitement de l'hypertension portale chez le cirrhotique. *Acta Chir. Belg.* 73:539, 1974.
62. James, J.H., Hodgman, J.M., Funovics, J.M., Fischer, J.E. Alterations in brain octopamine and brain tyrosine following portacaval anastomosis in rats. *J. Neurochem.* 27:223, 1976.

63. Johnston, G.W., Rodgers, H.W. A review of 15 years experience in the use of sclerotherapy in the control of acute haemorrhage from oesophageal varices. *Br. J. Surg.* 60:797, 1973.
64. Kardel, T., Lund, Y., Zander-Olsen, P., Möllgaard, V., Gammeltoft, A. Encephalopathy and portacaval anastomosis. *Scand. J. Gastroenterol.* 5:681, 1970.
65. Kardel, T., Nielsen, V., Kamp. Hepatic neuropathy: A clinical and electrophysiological study. *Acta Neurol. Scand.* 50:513, 1974.
66. Kardel, T. Neurologiske komplikationer til leverinsufficiens og portasystemisk shunt. *Fadl's Forlag*, København 1976.
67. Knill-Jones, R.P., Goodwill, C.J., Dayan, A.D., Williams, R. Peripheral neuropathy in chronic liver disease: Clinical electrodiagnostic and nerve biopsy findings. *J. Neurol. Neurosurg. Psychiat.* 35:22, 1972.
68. Lee, S.H., Fisher, B. Portacaval shunt in the rat. *Surgery* 50:668, 1961.
69. Linton, R.R., Ellis, D.S., Geary, J.E. Critical comparative analysis of early and late results of splenorenal and direct portacaval shunts performed in 169 patients with portal hypertension. *Ann. Surg.* 154:446, 1961.
70. Longmire, W.P. Jr. The surgical treatment of portal hypertension. *California Med.* 73:209, 1950.
71. Ludington, L.G. Study of 158 cases of esophageal varices. *Surg. Gyn. Obst.* 106:519, 1958.
72. Lunderquist, A., Vang, J. Transhepatic catheterization and obliteration of the coronary vein in patients with portal hypertension and esophageal varices. *N. Engl. J. Med.* 291: 646, 1974.
73. Lunderquist, A., Simert, G., Tylén, U., Vang, J. Follow-up of patients with portal hypertension and esophageal varices treated with percutaneous obliteration of the gastric vein. *Radiology* 122:59, 1977.
74. Maillard, J.N., Clot, P., Coste, T. Preoperative parameters influencing survival in patients with elective portacaval shunts. *Digestion* 10:129, 1974.

75. Malt, R.A., Szczerban, J., Malt, R.B. Risks in therapeutic portacaval and splenorenal shunts. *Ann. Surg.* 184:279, 1976.
76. Malt, R.A. Portasystemic venous shunts. *N. Engl. J. Med.* 295:24, 1976 and 295:80, 1976.
77. McCray, R.S., Martin, F., Amir-Ahmadi, H., Sheahan, D.G., Zamcheck, N. Erroneous diagnosis of haemorrhage from esophageal varices. *Amer. J. Dig. Dis.* 14:755, 1969.
78. Mikkelsen, W.P., Edmondson, H.A., Peters, R.L., Redeker, A.G., Reynolds, T.B. Extra- and intrahepatic portal hypertension without cirrhosis (hepatoportal sclerosis). *Ann. Surg.* 162:602, 1965.
79. Mikkelsen, W.P. Therapeutic portacaval shunt. Preliminary data on a controlled trial and morbid effects of acute hyalin necrosis. *Arch. Surg.* 108:32, 1974.
80. Mosimann, R., Rausis, C. La décompression élektive des varices oesogastriques par anastomose spléno-rénale distale. *Helv. Chir. Acta* 41:89, 1974.
81. Mosimann, R., Loup, P. Efficacy and risks of distal splenorenal shunt in the treatment of bleeding esophageal varices. *Am. J. Surg.* 133:163, 1977.
82. Mutchnick, M.G., Lerner, E., Conn, H.O. Portal-systemic encephalopathy and portacaval anastomosis: A prospective controlled investigation. *Gastroenterology* 66:1005, 1974.
83. Nabseth, D.C., Widrich, W.C., O'hara, T., Johnson, W.C. Flow and pressure characteristics of the portal system before and after splenorenal shunt. *Surgery* 78:739, 1975.
84. Paquet, K.J., Büsing, V., Kliems, G. Wandsklerosierung der Speiseröhre wegen akuter, konservativ unstillbarer und drohenden Varizenblutung. *Dtsch. Med. Wschr.* 102:59, 1977.
85. Pichancourt, M. Contribution to the study of the syndrome of portal hypertension: The tension of the fluids of ascites. Thesis, Paris 1913.
86. Pliam, M.B., Adson, M.A., Foulk, W.T. Conventional splenorenal shunts. A reconsideration. *Arch. Surg.* 110:588, 1975.

87. Ratnoff, O.B., Patek, A.J. Natural history of Laennec cirrhosis of the liver: Analysis of 386 cases. *Medicine* 21:207, 1942.
88. Resnick, R.H., Chalmers, T.C., Ishihara, A.M., Garceau, A.J., Callow, A.D., Schimmel, E.M., O'hara, E.T. and the Boston Inter-Hospital Liver Group. A controlled study of prophylactic portacaval shunts. A final report. *Ann. Int. Med.* 70:675, 1969.
89. Resnick, R.H., Iber, F.L., Ishihara, A.M. and the Boston Inter-Hospital Liver Group. A controlled study of the therapeutic portacaval shunt. *Gastroenterology* 67:843, 1974.
90. Rueff, B., Degos, F., Degos, J.D., Maillard, J.N., Prandi, D., Sicot, J., Fauvert, R., Benhamou, J.P. A controlled study of therapeutic portacaval shunt in alcoholic cirrhosis. *Lancet* 1:655, 1976.
91. Shaldon, S., Sherlock, S. Obstruction of the extra-hepatic portal system in childhood. *Lancet* 1:63, 1962.
92. Sherlock, S. Portal hypertension in childhood. *Proc. Roy. Soc. Med.* 55:767, 1962.
93. Siegel, S. Nonparametric statistics for the behavioral sciences. Mc Grain-Hill-Kogakusha Ltd, London 1956.
94. Siesjö, B.K., Holmin, T., Vang, J. Relation between changes in the acid-base and the energy metabolism of the brain in hepatic coma. *Exp. Biol. Med.* 4:42, 1971.
95. Silver, D., Puckett, C.L., Mc Neer, J.F. et al. Evaluation of selective trans-splenic decompression of gastro-oesophageal varices. *Am. J. Surg.* 127:30, 1974.
96. Simert, G., Bengmark, S., Börjesson, B., Eriksson, S., Hammar, E., Liedberg, G., Pettersson, K.I., Vang, J. Oesophagit och cardiafunktion hos patienter med oesophagusvaricer. *Svensk Kirurgi* 23:146, 1976.
97. Smith, G.J.W., Nyman, G.E. Manual till CWT-seriellt. Skand. Testförlaget, Stockholm 1972.
98. Summerskill, W.H.J., Davison, E.A., Sherlock, S., Steiner, R.E. *Quarterly J. Med* 49:245, 1956.

99. Snedecor, G.W., Cochran, W.G. Statistical methods 6, ed. Iowa 1965.
100. Texeira, E.D., Yu, H., Bergan, J.J. Nova tecnica na cirurgia da hipertensao porta: Estud experimental. Rev. Brasil. Cir. 53:443, 1967.
101. Thamm, M. Die portocavalen Venenverbindungen des Menschen. Zentralblatt für Chirurgie 39:1828, 1940.
102. Thomford, N.R., Sirinek, K.R., Martin, E.W.Jr. A series of 20 successful Warren shunts. Arch Surg. 110:584, 1974.
103. Thompson, W.P., Caughy, J.L., Whipple, A.O., Rousselot, L.M. Splenic vein pressure in congestive splenomegaly (Banti's syndrome). J. Clin. Inves. 16:571, 1937.
104. Turcotte, J.G., Lamberg, M.J. Variceal hemorrhage, hepatic cirrhosis and portacaval shunts. Surgery, 73:810, 1973.
105. Turner, J., Cuschieri, A., Shields, R. The prediction of the outcome of portacaval shunt using bromsulphthalein (BSP): A retrospective aspect, Br. J. Surg. 61:828, 1974.
106. Waldram, R., Davis, M., Nunnerly, H., Williams, R. Emergency endoscopy after gastrointestinal haemorrhage in 50 patients with portal hypertension. Br. Med. J. 4:94, 1974.
107. Walker, C.O., Speeg, K.V., Levison, J.D., Schenker, S. Cerebral acetylcholine, serotonin and norepinephrine in acute ammonia intoxication. Proc. Soc. Exp. Biol. Med. 136:668, 1971.
108. Warren, W.D., Zeppa, R., Fomon, J.J. Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. Ann. Surg. 166:437, 1967.
109. Warren, W.D., Salam, A.A., Hutson, D., Zeppa, R. Selective distal splenorenal shunt. Arch. Surg. 108,306, 1974.
110. Welch, C.S., Kiley, J.E., Reeve, T.S., Goodrich, E.O., Welch, H.F. Treatment of bleeding from portal hypertension in patients with cirrhosis of the liver. New Engl. J. Med. 254:493, 1956.

111. Wexler, M.J., Mac Lean, L.D. Massive spontaneous portal systemic shunting without varices. Arch. Surg. 110:995, 1975.
112. Whipple, A.O. Problems of portal hypertension in relation to the hepatosplenopathies. Ann. Surg. 122:449, 1945.
113. Wiechel, K.L. Tekniken vid percutan transhepatisk portapunktion (PTP). Nord. Med. 86:912, 1971.
114. Voorhees, A.B., Price, J.B., Britton, R.C. Porta-systemic shunting procedures for portal hypertension. Twenty-six years experience in adults with cirrhosis of the liver. Am. J. Surg. 119:501, 1970.
115. Zeegen, R., Drinkwater, J.E., Dawson, A.M. Method for measuring cerebral dysfunction in patients with liver disease. Brit. Med. J. 2:633, 1970.

PRINTING
ILLUSTRATION DEPARTMENT
DEPARTMENT OF SURGERY
UNIVERSITY OF LUND
1977